ORIGINAL ARTICLE

Lung cancer mortality among chromate production workers

R S Luippold, K A Mundt, R P Austin, E Liebig, J Panko, C Crump, K Crump, D Proctor

Aims: To assess mortality in 1997 among 493 former workers of a US chromate production plant employed for at least one year between 1940 and 1972.
Methods: Cohort members were followed for mortality to 31 December 1997. Standardised mortality ratios (SMRs) were calculated for selected cause specific categories of death including lung cancer. Lung cancer mortality was investigated further by calculation of SMRs stratified by year of hire, duration of employment, time since hire, and categories of cumulative exposure to Cr(VI).
Results: Including 51 deaths due to lung cancer, 303 deaths occurred. SMRs were significantly increased for all causes combined (SMR = 129), all cancers combined (SMR = 155), and lung cancer (SMR = 241). A trend test showed a strong relation between lung cancer mortality and cumulative hexavalent exposure. Lung cancer mortality was increased for the highest cumulative exposure categories ($\geq$1.05 to <2.70 mg/m^3-years, SMR = 365; $\geq$2.70 to 23 mg/m^3-years, SMR = 463), but not for the first three exposure groups. Significantly increased SMRs were also found for year of hire before 1960, 20 or more years of exposed employment, and latency of 20 or more years.
Conclusions: The finding of an increased risk of lung cancer mortality associated with Cr(VI) exposure is consistent with previous reports. Stratified analysis of lung cancer mortality by cumulative exposure suggests a possible threshold effect, as risk is significantly increased only at exposure levels over 1.05 mg/m^3-years. Though a threshold is consistent with published toxicological evidence, this finding must be interpreted cautiously because the data are also consistent with a linear dose response.

See end of article for authors' affiliations

Correspondence to:
Ms D M Proctor, Exponent, 320 Goddard Way, Suite 200, Irvine, CA 92618, USA;
dproctor@exponent.com

Accepted
11 October 2002

Occupational exposure to hexavalent chromium (Cr(VI)) compounds has been associated with a number of adverse health effects, most notably nasal irritation/perforation and lung cancer. Epidemiological studies have associated exposure in the chromate production industry with lung cancer for more than 50 years.[1–7] Cr(VI) has also been recognised to pose an inhalation cancer hazard in the chromate pigment production,[8] chrome plating,[9] and ferrochrome[10] industries.[11] Workers in chromate production plants have been exposed to a variety of Cr(VI) chemicals, typically including exposures to sparingly soluble calcium chromates, soluble mono- and dichromates, and chromic acid. All Cr(VI) compounds are classified as human carcinogens by the International Agency for Research on Cancer (IARC),[11] the National Institute of Occupational Safety and Health (NIOSH),[12] and the American Conference of Governmental Industrial Hygienists.[13] However, the sparingly soluble calcium chromate compounds, produced historically in chromate production plants using "high lime" processes, are considered to pose the greatest potential cancer hazard, based on intrabronchial implantation studies[14] and epidemiological evidence.[11 15]

Despite the available evidence of the carcinogenicity of Cr(VI), most epidemiological studies to date have not adequately characterised exposures to allow for quantitative risk assessment. Mancuso[2 3] quantified exposures to total and soluble chromium and used these measures to estimate exposures to trivalent and hexavalent chromium, but these

---

Main messages

- Many occupational studies have linked Cr(VI) exposure with lung cancer, but very few studies have quantified exposure to Cr(VI).
- The current study used quantitative measures of cumulative exposure to Cr(VI) and calculated SMRs, referenced to standard populations, and thus represents substantial improvements compared to previous studies of this chromate production plant.
- Lung cancer mortality was significantly increased for the two highest cumulative exposures categories only ($\geq$1.05 mg/m^3-years), suggesting the possibility of a threshold effect. This conclusion should be considered cautiously because a linear dose-response model is compatible with the data.
- Lung cancer mortality was not significantly increased for workers first exposed after 1960 when the plant started to use a lower lime mix in their process, generating less exposure to calcium chromate compounds, and improved industrial hygiene lowering Cr(VI) airborne exposures.
- These data provide an excellent opportunity for improved cancer risk assessment from chronic exposures as the cohort provides lung cancer mortality data for a reasonably stable, long term workforce.

Policy implications

- Regulatory agencies are currently reviewing available scientific studies of airborne Cr(VI) exposure and lung cancer for risk assessment and possible establishment of new exposure limits. This paper should be of direct interest and utility to these organisations.
- These data suggest that a threshold model for lung cancer might be valid and are consistent with toxicological and kinetic evidence for a threshold mechanism.

estimates were subject to a number of assumptions and have been criticised.[15–17] The recent study by Gibb and colleagues[7] assesses mortality stratified by cumulative exposure to Cr(VI) and reports results amenable to quantitative risk assessment and dose-response modelling. However, the study includes a very large fraction of short term workers, with more than half of the cohort working less than six months, and 40% working less than 90 days. Additionally, SMRs are presented by quartile of exposure, resulting in few data points from which to understand the dose-response relation for lung cancer.

This report describes the results of a retrospective cohort study of former employees of the chromate production plant in Painesville, Ohio that was studied previously by Mancuso.[2 3] The current study identifies and follows a non-overlapping and more recent cohort of employees. The plant studied in the current analysis also used a "high lime" production process, but reduced the amount of lime added to the roast mix starting in the 1950s. The mortality data from this study have been combined with a quantitative exposure reconstruction to quantify the relation between cumulative exposure and lung cancer. The current analysis reflects considerable improvements over the Mancuso studies,[2 3] including a more robust exposure analysis and a mortality assessment referenced to standard comparison populations.

The study objectives were to ascertain vital status, determine cause of death for identified decedents, and conduct mortality analysis using SMRs. SMRs were calculated for overall lung cancer mortality, and stratified by year of hire, duration of employment, time since hire, and categories of cumulative exposure to Cr(VI). All available historical exposure data were considered and, if appropriate, incorporated into a quantitative exposure assessment.

METHODS

The study cohort

Company records provided demographic and work history data that were used to identify a total of 1034 former workers potentially eligible for study. The following inclusion criteria were used to derive the study cohort: employed in the Painesville chromate production plant for at least one year beginning in 1940 or later, and did not work in any of the other facilities owned by the same company that used or produced Cr(VI). Exceptions were made for workers who subsequently worked at the plant in North Carolina because quantitative estimates of cumulative exposure were available for those employees. These inclusion criteria were established to ensure that Cr(VI) exposures to the study cohort would be estimated reliably for each worker.

Of 1034 potentially eligible employees initially identified, 493 met all of these criteria. Employees with exposure at other chromate plants were excluded (n = 6) because exposure data for those plants were not available. Similarly, workers employed before 1940 were excluded (n = 189) because no exposure data for these workers could be located, and the historical company files for workers of this time period were sparse. The identified employees who started in the 1930s are believed to be only a fraction of the workforce for that time, and represent only those still employed at the plant in the 1940s. Workers employed for less than one year were excluded (n = 328) because data regarding work history for these workers were very limited, and we reasoned that their exposures were too brief to have a major impact on cause of death. Furthermore, very short term workers may have different risk profiles than longer term workers, particularly concerning lifestyle factors such as nutrition, smoking, etc, as well as other occupational exposures. Of the 493 qualified for inclusion, 10 workers were missing valid dates of birth and could not be included in the SMR analyses. Another worker had implausible dates of birth and hire and was excluded. Thus, analysis results based on 482 employees are presented below.

Only limited information on other potential confounders such as smoking histories, or other occupational exposures was available, and was not used in the analysis. Smoking data were available on only 35% of the cohort. Most data regarding smoking was taken from annual surveys administered to all employees from 1960 to 1965 wherein employees were asked about current smoking status (yes/no). In a small percentage of cases, smoking status (smoker/non-smoker) was noted on the employee's medical file. Of the 35% for which smoking status records could be identified, approximately 78% were current smokers (answered yes on the survey at least once or were identified as a smoker on medical files). Information on race was also limited, and available primarily from death certificates.

Exposure assessment

The exposure assessment was based on over 800 air sampling measurements from 21 industrial hygiene surveys describing airborne concentrations of speciated Cr(VI), encompassing the years 1943 to 1971. A job-exposure matrix was constructed for 22 exposure areas for each month of plant operation from January 1940 to April 1972, when the plant closed. Gaps in the matrix—months between exposure surveys—were filled by computing from area sampling data the arithmetic mean concentration, averaged by exposure area, over three time periods (1940–49, 1950–64, 1965–71). These time periods were determined to coincide with process modifications at the plant that generally lowered worker exposures. Details of the methods describing the exposure assessment are planned for future publication.

Cumulative exposure categories (mg/m³-years) were formed in a time dependent manner using individual employment histories mapped to the job exposure matrix, so that each increment of person-years was assigned to the exposure category to which a death would be assigned should it have occurred at that time. The exposure reconstruction was conducted by researchers blinded to the vital status of the workers. Cut points for the five cumulative exposure groupings used in analysis were established to allow approximately equal numbers of expected respiratory cancer deaths in each category. Selection of cut points in this manner preserves the weighting of the population under study. Furthermore, it maximises stability for each estimate testing the null hypothesis of no deviation from the expected. Though trivalent chromium was also known to be present in the workplace, no exposure data for trivalent chromium were identified in the historical files.

Vital status searches

Several sources were used to ascertain the vital status of each member of the cohort, including the following:

- Company records, including death certificates
- Death certificates acquired from state offices of vital statistics
- Credit bureau database
- Social Security Administration's Death Master File (DMF)
- National Death Index Plus (NDI-Plus)
- Epidemiological Vital Status System of the Social Security Administration.

The last source also identified workers believed to be alive, based on several Social Security Administration data sources. Additionally, lists of former workers compiled earlier but not used by Mancuso, provided alternate sources of demographic, work history, and mortality data.

Cause of death coding

For each identified decedent, the underlying cause of death was acquired from NDI-Plus search results, the death

Table 1 Characteristics of Painesville, Ohio chromate production workers (n=482) and subset dead from lung cancer (n=51)

	Study cohort		Workers dead from lung cancer	
	n	%	n	%
Year of birth				
1877–1899	27	6	0	0
1900–1909	54	11	7	14
1910–1919	149	31	23	45
1920–1929	172	35	17	33
1930–1939	62	13	4	8
1940–1959	18	4	0	0
Year first exposed				
1940–1944	90	19	18	35
1945–1949	106	22	12	24
1950–1954	87	18	12	24
1955–1959	53	11	3	6
1960–1964	78	16	4	8
1965–1972	68	14	2	4
Length of employment (y)				
1–4	217	45	11	21
5–9	110	23	9	18
10–19	76	16	9	18
20–32	79	16	22	43
	Mean (SD)	Range	Mean (SD)	Range
Cumulative hexavalent exposure (mg/m^3·y)	1.58 (2.5)	0.003–23	3.28 (4.59)	0.06–23
Age at hire (y)	34.1 (11.0)	16.2–66.8	30.9 (9.6)	18.0–60.1
Length of follow up (y)	30.4 (14.4)	1.2–58.4	31.6 (11.8)	7.2–52.1

certificate, or both. The NDI database includes deaths reported since 1979. Death certificates were obtained from state offices of vital statistics and from company records, and were used to confirm the identity of the decedent, to provide missing data (for example, missing social security number (SSN)), and/or to obtain cause of death for pre-1979 deaths. For all death certificates obtained which did not have a corresponding NDI-Plus underlying cause of death code, the cause of death was coded to the four digit rubric of the ninth revision of the International Classification of Diseases (ICD-9).[18] Rules used to classify the underlying cause of death were the same as those defined by the National Center for Health Statistics.[19] Cause of death remains unknown for two cohort members deceased before 1979 because death certificates could not be located. For five decedents, the only source of cause of death information was the data compiled by Mancuso, which was recoded from the seventh to the ninth revision of the ICD for inclusion in the analyses. None of these five cohort members died of lung cancer.

Mortality analysis

The cohort was followed for mortality from 1 January 1941 to 31 December 1997. Person-years at risk (follow up) for each cohort member began one year after first exposure, and continued until the end of the study period, date of death, or date of truncation for those lost to follow up, whichever came first. Forty seven employees (10%) were coded as having unknown vital status as of the end of the study, and their follow up periods were truncated as of the date each was last known alive. For 43 workers, this was the date of separation from the chromate plant; the other four had substantial follow up that ended in 1997, just short of the end of the study period.

SMRs and 95% confidence intervals (CIs) were calculated for selected causes of death, including lung cancer, as well as all causes combined using reference rates for white males. Women comprised a very small portion of the cohort (n = 4), and race was known to be white for 94% (241 of 257) of decedents for whom we obtained a death certificate. SMR

analyses were conducted using ProSMR, a life table analysis module of the ProQuest database system (SoftWhere, Inc., Goshen, Massachusetts, USA and Applied Epidemiology, Inc., Amherst, Massachusetts, USA) and for cumulative exposure using EPICURE (Hirosoft International Corporation, Seattle, Washington, USA). The SAS system[20] was also used for selected analyses.

SMRs were calculated based on two different reference populations: the US population as a whole, and the population of the state of Ohio, where the chromate plant was located. Mortality rates for both Ohio and the United States for the years 1960 to 1994 were acquired from the NIOSH using CDC Wonder software for microcomputers.[21] For the calendar periods before 1960, US mortality rates were obtained directly from NIOSH (Kyle Steenland, PhD, personal communication), while Ohio rates for 1960–64 were used for the pre-1960 years because state rates were not readily available. The effect of this should be minimal, however, as less than one fourth of all person-years and only 6% (19 of 303) of all deaths occurred prior to 1960. We used 1990 to 1994 rates for the post-1994 rates, again because neither US nor Ohio rates were available for these years. Use of Ohio reference rates minimises bias that may occur from regional differences in mortality, which reflect environmental and lifestyle factors such as diet, smoking prevalence, and other factors.

In addition, lung cancer SMRs stratified separately by year of hire, duration of exposure, time since first exposure, and cumulative exposure group were calculated. Person-years were allocated to categories of cumulative exposure, duration of exposure, and time since first exposure in a time dependent manner. Thus, workers may contribute person-years to several exposure categories in the same analysis. A Poisson trend test for monotonic dose-response relation in the stratified SMRs was performed.[22]

RESULTS

Employee characteristics

Table 1 summarises the available demographic and employment history data. All but four of the workers were male.

Table 2 Overall mortality results for Painesville, Ohio chromate production workers, selected causes of death, follow up 1940–1997 (n=482, 14048 person-years)

Cause of death (ICD-9 codes)	Obs	Ohio reference rates			US reference rates		
		Exp	SMR	95% CI	Exp	SMR	95% CI
All causes (001–999)	303	235.0	129	115 to 144	225.6	134	120 to 150
All cancers (140–205)	90	57.9	155	125 to 191	54.3	166	133 to 204
Cancers of the respiratory system (160–165)	53	22.2	239	179 to 313	20.0	266	199 to 347
Larynx (161)	0	0.8	n/a	–	0.7	n/a	–
Trachea/bronchus/lung (162)	51	21.2	241	180 to 317	19.0	268	200 to 352
Other parts of respiratory system (160, 163–165)	2	0.2	941	114 to 3397	0.2	989	120 to 3574
Non-respiratory system cancers	37	35.7	104	73 to 143	34.3	108	76 to 148
Diseases of the heart	109	96.4	113	93 to 136	90.0	121	99 to 146
Other circulatory system diseases	30	21.0	143	96 to 204	19.9	151	102 to 216
Unknown causes of death	2	n/a	n/a	–	n/a	n/a	–

Almost half of the cohort was born before 1920, with 17% born before 1910. Age at hire averaged 34 years. Forty one per cent started working at the chromate plant during the 1940s, and 59% started before 1955.

Forty five per cent of employees worked less than five years in exposed jobs, and 16% worked 20 years or more. This measure of occupational tenure does not include time spent in unexposed jobs. Length of follow up averaged 30 years, and ranged from 1 to 58 years. The average age at death for the 303 decedents was 66 years. Follow up for the 482 employees in the analysis totaled 14 048 person-years.

Exposure characteristics
Table 1 presents cumulative exposure data. The average cumulative exposure was 1.58 mg/m^3-y, and ranged from 0.003 to 23 mg/m^3-y (table 1). Of the 482 cohort members included in analyses, 60% (290/482) accumulated an estimated exposure of 1.00 mg/m^3-y or less (data not shown).

Vital status and cause of death
Based on all data sources, 62% (303/492) of the study cohort were identified as deceased as of 31 December 1997. Because cause of death could not be determined for two decedents they were included in the all cause analysis, but could not be included in any of the cause specific analyses. Cancer deaths comprised 30% (n = 90) of known causes, with 57% (n = 51) of these identified as lung cancer.

Characteristics of employees deceased from lung cancer
Table 1 contains summary statistics for the 51 cohort members who died of lung cancer. Nearly 60% of employees that died of lung cancer were born before 1920. For this group, the average age at the start of employment in the chromate plant was approximately 31 years. Thirty five percent (n = 18) started working at the plant between 1940 and 1944, and 82% started before 1955. Only 21% worked one to five years (12–60 months), but 43% worked 20 years or more (240 months). The average age at death for this group was 62 years. Cumulative exposure averaged 3.28 mg/m^3-y for lung cancer decedents, in contrast to 1.55 mg/m^3-y for the cohort as a whole.

Mortality results
Table 2 presents overall SMR results and 95% CIs for selected causes of death based on both Ohio and US mortality rates. Additional SMRs referencing Ohio rates were calculated for lung cancer deaths stratified separately by year of hire, duration of employment, time since first exposure, and cumulative exposure (see table 3).

Mortality from all causes showed a statistically significant excess of 29% (SMR = 129, 95% CI 115 to 144; table 2), based on Ohio mortality rates. Results using United States rates were

similar, but the SMRs tended to be slightly higher, suggesting that Ohio mortality rates were higher for white males during this period. Mortality from all cancers also showed a statistically significant excess (SMR = 155, 95% CI 125 to 191). While much of the excess mortality can be attributed to excess cancers, there was also an approximately 20% excess of non-cancer deaths (results not shown). Mortality from heart diseases and other circulatory system diseases were slightly increased (SMR = 113, 95% CI 93 to 136; and SMR = 143, 95% CI 96 to 204, respectively) based on Ohio reference rates. These results show the lack of a healthy worker effect in this cohort and suggest that the overall health of the study cohort was less favourable than typical working populations or the overall general population.

When all non-respiratory system cancer mortality was examined, no excess risk was found, based on 37 observed and 35.7 expected deaths (SMR = 104, 95% CI 73 to 143). As seen in table 2, the 51 deaths from lung cancer represent over twice the expected number (21.2) for the cohort, resulting in an SMR of 241 (95% CI 180 to 317). There were no deaths due to laryngeal cancer. There were two deaths from cancer of other parts of the respiratory system (specifically, the pleura, unspecified and the maxillary sinus) with only 0.2 expected.

Stratified lung cancer SMRs
Increased lung cancer SMRs were also seen for employees hired during the first two decades of follow up (table 3). Employees hired between 1940 and 1949 showed the highest excess of lung cancer deaths (SMR = 326, 95% CI 220 to 465) based on 30 observed and 9.2 expected deaths. Those hired 1950 to 1959 showed a similar excess based on 15 observed and 5.5 expected deaths (SMR = 275, 95% CI 154 to 454). The last stratum showed that lung cancer mortality for those hired between 1960 and 1971 was essentially as expected (6 observed and 6.5 expected deaths). For this group, follow up ranged from 27 to 38 years, and cumulative exposure averaged 0.30 mg/m^3-y. In contrast, average cumulative exposure was 1.00 mg/m^3-y for employees hired 1950 to 1959, and 2.96 mg/m^3-y for those hired 1940 to 1949.

SMRs varied by categories of employment duration (table 3). Although the point estimates were increased for each stratum, a dramatically increased SMR of 497 (95% CI 328 to 723) was generated for employees working 20 or more years. Lung cancer SMRs stratified by time since first exposure are also presented in table 3. Again, although increased point estimates were evident for every stratum, the highest and statistically significant estimates occurred at 20 years or more since first exposure. This finding is consistent with the known long latency period for lung cancer, as 44 (86%) of the 51 lung cancer deaths occurred 20 or more years after initial exposure.

Table 3 also presents SMRs for lung cancer, stratified by five cumulative exposure groups, using Ohio reference rates. It was

Table 3 Stratified lung cancer mortality results for Painesville, Ohio chromate production workers, follow up 1940 to 1997, Ohio white male reference rates (n=482, 14048 person-years)

Stratification variable	Employees*	Person-years	Obs	Exp	SMR	95% CI	Trend†
Year of hire							0.005
1940–1949	196	6598	30	9.2	326	220 to 465	
1950–1959	140	3897	15	5.5	275	154 to 454	
1960–1971	146	3553	6	6.5	92	34 to 201	
Duration of employment (y)*							0.0001
1–4	482	5311	9	6.6	137	62 to 260	
5–9	314	3576	8	5.0	160	69 to 314	
10–19	201	2970	7	4.1	169	68 to 349	
20–32	106	2191	27	5.4	497	328 to 723	
Time since first exposure (y)*							0.12
0–9	482	4064	2	1.5	131	16 to 473	
10–19	430	4015	5	3.7	136	44 to 317	
20–29	366	3104	16	5.8	277	158 to 449	
30 or more	257	2865	28	10.2	275	183 to 398	
Cumulative hexavalent exposure, mg/m³-y‡							0.00002
0.00–0.19		2952	3	4.5	67	14 to 196	
0.20–0.48		2369	8	4.4	184	79 to 362	
0.49–1.04		3077	4	4.4	91	25 to 234	
1.05–2.69		3220	16	4.4	365	208 to 592	
2.70–23		2482	20	4.3	463	283 to 716	

*The number of employees in the analyses for *Duration of employment* and *Time since first exposure* represent the number contributing person-years to each stratum. The time dependent method of person-years accumulation means that all employees contribute person-years to the lowest stratum, while fewer contribute to each successive higher stratum.
†p values from two sided Poisson trend test for an effect of exposure.
‡Person-years for the cumulative exposure strata total 14100, due to use of a different application for this analysis.

expected that United States rates would generate similar results, with slightly higher SMRs. The Poisson test for trend indicated a positive exposure-response relation between lung cancer mortality and cumulative hexavalent exposure categories (p = 0.00002). However, examination of the cumulative exposure categories shows that 36 of the 51 (71%) lung cancer deaths occurred among workers in the two highest exposure categories (that is, 1.05 mg/m³-y or higher). SMRs were statistically significantly increased for these two categories (SMR = 365, 95% CI 208 to 592; and SMR = 463, 95% CI 283 to 716, respectively). Only 15 lung cancer deaths occurred among workers in the three lowest exposure categories, resulting in estimates with wide confidence intervals. The results for the lowest three exposure categories, with less than 1.05 mg/m³-y, indicated that lung cancer mortality was not significantly different from that of the reference population.

DISCUSSION

The current mortality study benefits from an exposure assessment that represents a clear improvement over previous studies of chromate chemical production workers from the chromate plant in Painesville, Ohio[2 3] and other locations. The Mancuso studies of this chromate plant provide the basis for the current inhalation cancer dose-response assessment used by the Environmental Protection Agency to evaluate the risk from environmental Cr(VI) exposures.[23] Several methodological and study design features differentiate the current study from previous investigations of this plant.[2 3] The Mancuso cohort was comprised of workers hired from 1931 to 1937, yet characterisation of exposure was based on a single industrial hygiene area survey conducted 12–18 years later in 1949.[24] That survey did not quantify Cr(VI); rather, only total and soluble chromium were reported from which the Cr(VI) fraction was estimated. Furthermore, the survey is believed to underestimate total chromium exposures for the years prior to 1949.[24 25]

The current exposure reconstruction utilised multiple area surveys, conducted from 1943 to 1971, to quantify exposure and used data that were speciated for Cr(VI). A further distinction is that this cohort of workers employed after 1939 did not overlap with the Mancuso cohort of workers employed between 1931 and 1937. A criticism of the previous studies is

that the investigator did not assess lung cancer mortality relative to a standard comparison population.[16] In this report we presented SMRs based on both US and Ohio reference populations, for selected causes of death including lung cancer.

The finding of a twofold excess of lung cancer among this cohort is consistent with previous studies of chromium workers exposed in plants using a high lime production process. Korallus and colleagues[5] found an increased SMR for lung cancer of 227 (95% CI 178 to 285), while Davies and colleagues[4] reported an SMR of 197 (175 observed, 88.97 expected) for cohorts working in plants using a high lime production process, similar to that used at the Painesville plant. Another finding consistent with these two studies is that workers who started at the Painesville plant after the switch to a lower lime mix in 1960 have not, to date, experienced an excess of lung cancer mortality (6 observed, 6.5 expected, table 3).

We found a statistically significant excess of mortality from all cancers, which can be attributed primarily to the excess due to lung cancer. We did not detect a healthy worker effect (that is, the tendency for working populations to experience lower mortality rates than the general population) in this cohort (see table 2), which suggests that the cohort's overall health was less favourable than that of the population of Ohio, or the USA as a whole. However, the healthy worker effect is not usually reflected in cancer mortality and tends to diminish with increasing length of follow up, therefore a strong healthy worker effect would not be expected in this cohort. Further investigation of other non-cancer outcomes, such as heart and circulatory disease mortality were analysed for this cohort. Evidence of deficits in these particular diseases is often associated with the healthy worker effect. For diseases of the heart, the category with the largest number of deaths (n = 109, 36% of all deaths), the SMR was slightly increased (SMR = 113, 95% CI 93 to 136) but not statistically significant. Similarly, deaths due to circulatory system diseases were increased (SMR = 143, 95% CI 96 to 204), based on 30 deaths (10% of all deaths). Combined, these results suggest that this occupational cohort experienced below average health most likely related to smoking and may also include factors such as diet, physical activity and other lifestyle indicators.

Furthermore, the limited smoking data available for this study suggests that a high proportion of employees smoked.

Unfortunately, the smoking data for this cohort were not sufficiently complete for use in the analysis as only 35% of the study cohort was represented. The available data were from annual surveys administered to all employees during the years 1960 to 1965 only. Employees were asked about current smoking status and responses indicated that a high proportion, approximately 78%, were current smokers (answered yes on the survey at least once). Though not reported, the proportion of ever smokers would be even higher. Additionally, the proportion of self reported smokers was similar in each cumulative exposure group, and ranged from 73% to 86%. It is likely that the survey results are representative of the entire cohort, and our finding of a lack of a healthy worker effect in this cohort could be linked to the high level of smoking. It is unlikely, however, that confounding by smoking could drive the dose-response pattern observed.

Examination of lung cancer mortality by year of hire in this study indicated that 45 of the 51 deaths (88%) occurred in workers hired prior to 1960 (table 3), while 30 (59%) of these occurred in workers hired 1940 to 1950. A trend of decreasing risk was evident, with no excess mortality detected among those hired after 1960. Strata cut points for analysis were selected to coincide approximately with process changes implemented at the plant. In 1950 the plant was renovated (shifting of some operations from one building to another) and upgraded with new equipment.[24] A process change was implemented starting in 1964 that created a closed system through which the roast was discharged directly from the kilns to the main leaching area. The lack of an increase in lung cancer risk seen in the last stratum, hire dates 1960 to 1971, is interesting as the follow up period for these workers was adequate to detect an excess risk, and may reflect a lower risk due to reductions in the Cr(VI) exposures or the conversion to a lower lime process.

The analyses stratified by duration of employment and time since first exposure indicate a consistency of results among those employed the longest and with the longest elapsed time since first exposure. The latter suggests a latency period of approximately 20–35 years, which is compatible with other research.[2 5 6 15]

Stratified analysis of lung cancer mortality showed a trend of increasing mortality with higher cumulative exposure levels (table 3). To evaluate a possible dose-response, a linear model was evaluated using a χ^2 test. This test showed no significant departure from linearity (χ^2 goodness of fit of linear model, p = 0.23), indicating that a linear model may be compatible with the data. However, these SMRs are also consistent with a threshold effect, as the risk increased substantially at cumulative exposure levels above 1.05 mg/m^3-y (60% of the exposed cohort). This conclusion should be considered cautiously given the small number of lung cancer deaths observed, especially in the lower exposure categories.

Recently, Gibb and colleagues[7] reported SMRs by four cumulative exposure levels for a cohort of chromate production workers working 1950 to 1974 at a US plant in Baltimore, Maryland. Exposures ranged from no exposure to a maximum of 2.73 mg Cr(VI)/m^3-y (converted from the reported 5.25 mg CrO$_3$/m^3-y). Though the overall SMR for lung cancer was significantly increased as compared to the standardised US reference population (SMR = 180, 95% CI 149 to 214), the stratified analysis yielded statistically significantly increased SMRs for the two highest cumulative exposure categories only (≥0.0046 mgCr(VI)/m^3-y, converted). Interestingly, in general, cumulative exposures to Cr(VI) among the Baltimore cohort were notably lower than those of the Painesville cohort, and the entire Painesville cohort falls in and above the highest exposure quartile reported for the Baltimore cohort. The lowest level of exposure which resulted in a statistically significant risk for the total Baltimore cohort was the third quartile, with a mean exposure level of 0.016 mg Cr(VI)/m^3-y (converted from presented units of 0.030 mg CrO$_3$/m^3-y). This

cumulative exposure level is far below the level at which a significant risk was observed among the Painesville cohort (1.05 mg/m^3-y).

Comparison of our results with the Baltimore cohort study may be difficult for several reasons. Although the Baltimore cohort is considerably larger than this Painesville cohort (2357 versus 492 workers, respectively), very short term workers were included in the Baltimore cohort, including some that were reported to have no exposure. More than half of the Baltimore cohort worked less than six months, and 990 workers (42%) worked less than 90 days. In fact, only 589 (25%) worked two or more years. In contrast, over half (54%) of the cohort from the Painesville plant worked six or more years in the plant. Unlike the Baltimore study, Painesville employees with less than one year of employment were excluded from the current study. Lifestyle factors may differ considerably for short term employees, and other (unmeasured) occupational exposures may be more likely to exist. Short term workers may have different risk profiles than longer term workers. Overall, the Painesville cohort represents a more stable, longer term workforce and provides data that may be used to better characterise long term (chronic) exposures to Cr(VI).

Several limitations must be considered in interpreting the current results. Although the exposure assessment represents a major improvement in methodology, it is not without limitations, including the absence of personal monitoring data, sparse industrial hygiene area measures in the 1940s, and gaps in work history for some cohort members. Use of cumulative exposure may obscure effects involving intensity and duration, as well as temporal sequencing, because it incorporates all these factors into an absolute amount of exposure.[26]

Further, reconstructing an employee cohort of a closed facility of a company that is no longer in existence presented difficulties, and data gaps still exist for some cohort members. A total of 10 (2%) employees were missing date of birth at the close of the study, while another had implausible dates, and could not be included in the SMR analyses. A valid SSN was not found for 48 of the 493 employees eligible for the study (10%), and seven of these workers were missing both SSN and date of birth. Vital status was unknown for 47 of the 482 (10%) workers in the cohort, and person years at risk were censored substantially for 43 of these workers (that is, most were censored in the 1950s and 1960s, as of their date of separation from the company). Most of those censored had insufficient data for key fields (usually SSN) which limited the vital status searches that could be completed for these workers. Additionally, some of those lost to follow up likely represent pre-1979 deaths which are more difficult to trace. Information on potential confounders, such as smoking was also limited, and precluded our ability to assess their effects.

Cr(VI) has long been known to cause lung cancer and, as expected, this report supplies yet more evidence. However, there has been considerable uncertainty regarding the dose-response relation between Cr(VI) and lung cancer. Of the very few studies that have characterised exposure, this epidemiological study is the first to suggest that the data could be consistent with a threshold effect between Cr(VI) exposure (a surrogate for dose) and lung cancer. The biological basis for a threshold effect rests on the capacity of the lung to reduce Cr(VI) to the non-carcinogenic trivalent state.[27 28] This finding must be interpreted cautiously given the limitations described above, as well as the significant linear trend of the dose-response. Nonetheless, these findings provide important evidence in the process of elucidating the dose-response relation between Cr(VI) and lung cancer.

ACKNOWLEDGEMENTS

and technical support. Robert Bilgrad of the National Death Index was helpful in guiding us through the NDI application process. We acknowledge the efforts of the Vital Statistics Offices of the following states in filling our requests for death certificates: Arizona, Florida, Indiana, Iowa, Maryland, Michigan, New Jersey, New York, North Carolina, Ohio, Pennsylvania, South Carolina, Tennessee, Texas, Virginia, and West Virginia. We are particularly grateful to Paula Holbrook of the Ohio Department of Health, who was especially helpful in expediting our request.

. . . .

Authors' affiliations
R S Luippold, K A Mundt, R P Austin, Applied Epidemiology, Inc., PO Box 2424, Amherst, Massachusetts 01004, USA
E Liebig, J Panko, AMEC Earth and Environmental, Gulf Tower, 707 Grant Street, Suite 81, Pittsburgh, Pennsylvania 15219, USA
C Crump, 5307 Ravenna Place, NE, #3, Seattle, Washington 98105, USA
K Crump, Environ, 2220 South Vienna, Ruston, Louisiana 71270, USA
D Proctor, Exponent, 320 Goddard Way, Suite 200, Irvine, California 92618, USA

REFERENCES
1 **Machle W**, Gregorius F. Cancer of the respiratory system in the United States chromate-producing industry. *Public Health Rep* 1948;**63**:1114–27.
2 **Mancuso TF**. Consideration of Chromium as an Industrial Carcinogen. International Conference on Heavy Metals in the Environment, Toronto, Ontario, Canada, 1975: 343–56.
3 **Mancuso TF**. Chromium as an industrial carcinogen: Part I. *Am J Ind Med* 1997;**31**:129–39.
4 **Davies JM**, Easton DF, Bidstrup PL. Mortality from respiratory cancer and other causes in United Kingdom chromate production workers. *Br J Ind Med* 1991;**48**:299–313.
5 **Korallus U**, Ulm K, Steinmann-Steiner-Haldenstaett W. Bronchial carcinoma mortality in the German chromate-producing industry: the effects of process modification. *Int Arch Occup Environ Health* 1993;**65**:171–8.
6 **Rosenman KD**, Stanbury M. Risk of lung cancer among former chromium smelter workers. *Am J Ind Med* 1996;**29**:491–500.
7 **Gibb HJ**, Lees PS, Pinsky PF, *et al*. Lung cancer among workers in chromium chemical production. *Am J Ind Med* 2000;**38**:115–26.
8 **Hayes RB**, Sheffet A, Spirtas R. Cancer mortality among a cohort of chromium pigment workers. *Am J Ind Med* 1989;**16**:127–33.
9 **Sorahan T**, Harrington JM. Lung cancer in Yorkshire chrome platers, 1972–97. *Occup Environ Med* 2000;**57**:385–9.
10 **Moulin JJ**, Portefaix P, Wild P, *et al*. Mortality study among workers producing ferroalloys and stainless steel in France. *Br J Ind Med* 1990;**47**:537–43.
11 **International Agency for Research on Cancer (IARC)**. *Chromium, nickel and welding*. Lyon, France: IARC, 1990.
12 **US Department of Health and Human Services**. *NIOSH pocket guide to chemical hazards*. Cincinnati: US Department of Health and Human Services, 1990.
13 **American Conference of Government and Industrial Hygienists**. *TLVs and BEIs: threshold limit values for chemical substances and physical agents biological exposure indices*. Cincinnati: ACGHI, 1997.
14 **Levy LS**, Martin PA, Bidstrup PL. Investigation of the potential carcinogenicity of a range of chromium containing materials on rat lung. *Br J Ind Med* 1986;**43**:243–56.
15 **Langard S**. One hundred years of chromium and cancer: a review of epidemiological evidence and selected case reports. *Am J Ind Med* 1990;**17**:189–215.
16 **Mundt KA**, Dell LD. Carcinogenicity of trivalent and hexavalent chromium. *The Occupational and Environmental Medicine Report* 1997;**11**:95–100.
17 **Proctor DM**, Panko JM, Finley BL, *et al*. Need for improved science in standard setting for hexavalent chromium. *Regul Toxicol Pharmacol* 1999;**29**(2 Pt 1):99–101.
18 **World Health Organisation**. *Manual of the international classification of diseases, injuries and causes of death, ninth revision*. Geneva, Switzerland: World Health Organisation, 1977.
19 **National Center for Health Statistics**. *Instruction manual, part 2a: instructions for classifying the underlying cause of death*. Hyattsville, MD: US Department of Health and Human Services, 1992.
20 **SAS Institute**, *Inc*. The SAS system, version 6.12. Cary, NC, 1996.
21 **Friede A**, Reid JA, Ory HW. CDC WONDER: a comprehensive on-line public health information system of the Centers for Disease Control and Prevention. *Am J Public Health* 1993;**83**:1289–94.
22 **Breslow NE**, Day NE. *Statistical Methods in Cancer Research. Volume II: The design and analysis of cohort studies*. Lyon, France: IARC Press, 1987.
23 **US Environmental Protection Agency**. Integrated risk information system (IRIS). *Toxicological review of hexavalent chromium*. Washington, DC, 1998.
24 **Bourne HG**, Yee HT. Occupational cancer in a chromate plant—an environmental appraisal. *Ind Med Surg* 1950;**19**:563–7.
25 **US Environmental Protection Agency**. *Health assessment document for chromium*. Research Triangle Park, NC: Environmental Criteria and Assessment Office, 1984.
26 **Checkoway H**, Pearce N, Crawford-Brown DJ. *Research methods in occupational epidemiology*. New York: Oxford University Press, 1989.
27 **Jones RE**. Hexavalent chrome: threshold concept for carcinogenicity. *Biomed Environ Sci* 1990;**3**:20–34.
28 **De Flora S**. Threshold mechanisms and site specificity in chromium(VI) carcinogenesis. *Carcinogenesis* 2000;**21**:533–41.